Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma

Ascierto, Paolo A ; Dummer, Reinhard ; Gogas, Helen J ; Flaherty, Keith T ; Arance, Ana ; Mandala, Mario ; Liszkay, Gabriella ; Garbe, Claus ; Schadendorf, Dirk ; Krajsova, Ivana ; Gutzmer, Ralf ; de Groot, Jan Willem B ; Loquai, Carmen ; Gollerkeri, Ashwin ; Pickard, Michael D ; Robert, Caroline

Abstract: BACKGROUND BRAF/MEK inhibitor combinations are established treatments for BRAF V600-mutant melanoma based on demonstrated benefits on progression-free survival (PFS) and overall survival (OS). Here, we report an updated analysis of the COLUMBUS (COmbined LGX818 [encorafenib] Used with MEK162 [binimetinib] in BRAF mutant Unresectable Skin cancer) trial with long-term follow-up. METHODS In part 1 of the COLUMBUS trial, 577 patients with advanced/metastatic BRAF V600-mutant melanoma, untreated or progressed after first-line immunotherapy, were randomised 1:1:1 to 450 mg of encorafenib QD + 45 mg of binimetinib BID (COMBO450) vs 960 mg of vemurafenib BID (VEM) or 300 mg of encorafenib ENCO QD (ENCO300). An updated analysis was conducted that included PFS, OS, objective response rate, safety and tolerability and analyses of results by prognostic subgroups. RESULTS At data cutoff, there were 116, 113 and 138 deaths in the COMBO450, ENCO300 and VEM treatment arms, respectively. The median OS was 33.6 months (95% confidence interval [CI], 24.4-39.2) for COMBO450, 23.5 months (95% CI, 19.6-33.6) for ENCO300 and 16.9 months (95% CI, 14.0-24.5) for VEM. Compared with VEM, COMBO450 decreased the risk of death by 39% (hazard ratio [HR], 0.61; 95% CI, 0.48-0.79). The updated median PFS for COMBO450 was 14.9 months (95% CI, 11.0-20.2), ENCO300 was 9.6 months (95% CI, 7.4-14.8) and VEM was 7.3 months (95% CI, 5.6-7.9). PFS was longer for COMBO450 vs VEM (HR, 0.51; 95% CI, 0.39-0.67). Landmark OS and PFS results show consistent results for each year analysed. Subgroups all favoured COMBO450 vs VEM. CONCLUSIONS Updated PFS and OS results for COMBO450 from the COLUMBUS trial demonstrate a long-term benefit in patients with advanced BRAF V600-mutated melanoma.

DOI: https://doi.org/10.1016/j.ejca.2019.11.016

Ascierto, Paolo A; Dummer, Reinhard; Gogas, Helen J; Flaherty, Keith T; Arance, Ana; Mandala, Mario; Liszkay, Gabriella; Garbe, Claus; Schadendorf, Dirk; Krajsova, Ivana; Gutzmer, Ralf; de Groot, Jan Willem B; Loquai, Carmen; Gollerkeri, Ashwin; Pickard, Michael D; Robert, Caroline (2020). Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. European Journal of Cancer, 126:33-44.
DOI: https://doi.org/10.1016/j.ejca.2019.11.016

European Journal of Cancer 126 (2020) 33–44

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with *BRAF* V600–mutant melanoma☆

Paolo A. Ascierto [a,*], Reinhard Dummer [b], Helen J. Gogas [c], Keith T. Flaherty [d], Ana Arance [e], Mario Mandala [f], Gabriella Liszkay [g], Claus Garbe [h], Dirk Schadendorf [i,j], Ivana Krajsova [k], Ralf Gutzmer [l], Jan Willem B. de Groot [m], Carmen Loquai [n], Ashwin Gollerkeri [o], Michael D. Pickard [o], Caroline Robert [p]

[a] *Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy*
[b] *Department of Dermatology, University Hospital Zürich Skin Cancer Center and University Zürich, Zürich, Switzerland*
[c] *Department of Internal Medicine, National and Kapodistrian University of Athens, Laikon Hospital, Athens, Greece*
[d] *Cancer Center, Massachusetts General Hospital, Boston, MA, USA*
[e] *Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain*
[f] *Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy*
[g] *Department of Dermatology, National Institute of Oncology, Budapest, Hungary*
[h] *Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany*
[i] *Department of Dermatology, University Hospital Essen, Essen, Germany*
[j] *German Cancer Consortium, Heidelberg, Germany*
[k] *Department of Dermato-oncology, University Hospital Prague and Charles University First Medical Faculty, Prague, Czech Republic*
[l] *Department of Dermatology and Allergy, Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany*
[m] *Department of Medical Oncology, Isala, Zwolle, Netherlands*
[n] *Department of Dermatology, University Medical Center Mainz, Mainz, Germany*
[o] *Pfizer Inc., Boulder, CO, USA*
[p] *Service of Dermatology, Department of Medicine and Paris-Sud University, Gustave Roussy, Villejuif, France*

Received 16 November 2019; accepted 20 November 2019
Available online 2 January 2020

☆ Sponsor: This study was sponsored by Pfizer Inc. (formerly Array BioPharma, Inc).
* *Corresponding author*: Paolo Ascierto, MD. Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy.
E-mail address: paolo.ascierto@gmail.com (P.A. Ascierto).

https://doi.org/10.1016/j.ejca.2019.11.016

KEYWORDS
BRAF V600–mutant melanoma;
Overall survival;
BRAF inhibitor;
MEK inhibitor

Abstract ***Background:*** BRAF/MEK inhibitor combinations are established treatments for *BRAF* V600–mutant melanoma based on demonstrated benefits on progression-free survival (PFS) and overall survival (OS). Here, we report an updated analysis of the COLUMBUS (COmbined LGX818 [encorafenib] Used with MEK162 [binimetinib] in *BRAF* mutant Unresectable Skin cancer) trial with long-term follow-up.
Methods: In part 1 of the COLUMBUS trial, 577 patients with advanced/metastatic *BRAF* V600–mutant melanoma, untreated or progressed after first-line immunotherapy, were randomised 1:1:1 to 450 mg of encorafenib QD + 45 mg of binimetinib BID (COMBO450) vs 960 mg of vemurafenib BID (VEM) or 300 mg of encorafenib ENCO QD (ENCO300). An updated analysis was conducted that included PFS, OS, objective response rate, safety and tolerability and analyses of results by prognostic subgroups.
Results: At data cutoff, there were 116, 113 and 138 deaths in the COMBO450, ENCO300 and VEM treatment arms, respectively. The median OS was 33.6 months (95% confidence interval [CI], 24.4–39.2) for COMBO450, 23.5 months (95% CI, 19.6–33.6) for ENCO300 and 16.9 months (95% CI, 14.0–24.5) for VEM. Compared with VEM, COMBO450 decreased the risk of death by 39% (hazard ratio [HR], 0.61; 95% CI, 0.48–0.79). The updated median PFS for COMBO450 was 14.9 months (95% CI, 11.0–20.2), ENCO300 was 9.6 months (95% CI, 7.4–14.8) and VEM was 7.3 months (95% CI, 5.6–7.9). PFS was longer for COMBO450 vs VEM (HR, 0.51; 95% CI, 0.39–0.67). Landmark OS and PFS results show consistent results for each year analysed. Subgroups all favoured COMBO450 vs VEM.
Conclusions: Updated PFS and OS results for COMBO450 from the COLUMBUS trial demonstrate a long-term benefit in patients with advanced *BRAF* V600–mutated melanoma.

1. Introduction

Based on improved overall survival (OS) and the tolerability profile relative to BRAF inhibitor monotherapy, combination BRAF/MEK inhibitor therapy is now the standard of care in *BRAF* V600E–mutant locally advanced or metastatic melanoma [1–3]. Encorafenib is a highly selective ATP-competitive BRAF inhibitor developed with unique pharmacological properties aimed at improving efficacy and tolerability over other approved BRAF inhibitors [4]. Preclinical studies have demonstrated increased potency against *BRAF* V600 mutations [5–7] and extended duration of target inhibition and shorter serum half-life that may delay resistance and translate to improved tolerability [4–6]. Binimetinib is a potent, selective allosteric, ATP-uncompetitive MEK1/2 inhibitor that has a shorter half-life than other MEK1/2 inhibitors, which may provide more rapid resolution of toxicity upon dose interruption [8].

The phase 3 COLUMBUS study compared 450 mg of encorafenib once daily (QD) + 45 mg of binimetinib twice daily (BID, COMBO450) vs 300 mg of encorafenib QD (ENCO300) or 960 mg of vemurafenib BID (VEM) in patients with *BRAF* V600E/K–mutant melanoma [9,10]. Compared with VEM, COMBO450 extended median progression-free survival (PFS) (7.3 vs 14.9 months; hazard ratio [HR], 0.54; 95% confidence interval [CI], 0·41–0·71) and median overall survival (16.9 vs 33.6 months; HR, 0.61; 95% CI, 0·47–0·79). Mature landmark analyses on PFS and OS, as well as analyses of some prognostic subgroups, require long-term follow-up.

Here, we report an updated analysis of the COLUMBUS trial in patients with *BRAF* V600 mutant locally advanced unresectable or metastatic melanoma in an updated landmark analysis.

2. Methods

2.1. Trial design

The design and primary analyses have been published [9,10]; NCT01909453). Briefly, COLUMBUS was a two-part, multicenter, randomised, open-label, phase 3 study with patients enrolled from 162 hospitals in 28 countries. Enrolment for part 1 occurred between December 30, 2013, and April 10, 2015. In part 1 of COLUMBUS, 577 patients with advanced/metastatic *BRAF* V600–mutant melanoma, untreated or progressed after first-line immunotherapy, were randomised 1:1:1 to COMBO450 vs VEM or ENCO300.

2.2. Patient eligibility

Key eligibility criteria included that patients had to be at least 18 years of age with a histologically confirmed diagnosis of locally advanced, unresectable or metastatic

cutaneous melanoma or unknown primary melanoma classified as American Joint Committee on Cancer (AJCC) stage IIIB, IIIC or IV; be treatment naive or had progressed on or after previous first-line immunotherapy; *BRAF* V600E or *BRAF* V600K mutation or both in tumour tissue as ascertained by central genetic mutation analysis with the bioMerieux THxID BRAF diagnostic test before enrolment; have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and/or have adequate bone marrow, organ function and laboratory parameters and at least one measurable lesion in accordance with guidelines based on Response Evaluation Criteria in Solid Tumors. Patients were ineligible if they had untreated central nervous system lesions; uveal or mucosal melanoma; a history of leptomeningeal metastases; Gilbert syndrome; history, current evidence or risk of retinal vein occlusion; previous BRAF inhibitor or MEK inhibitor treatment; previous use of systemic chemotherapy, extensive radiotherapy or an investigational agent other than previous immunotherapy for locally advanced, unresectable or metastatic melanoma.

2.3. End-points and assessments

An updated analysis including PFS, OS, objective response rate (ORR), safety and tolerability and analyses of results by prognostic subgroups including elevated lactate dehydrogenase (LDH) and degree of organ involvement were conducted after an additional 12 months' follow-up after the initial OS analysis. Additional details on methodology can be found in previous publications [9,10]. Safety was analysed in patients who received at least one dose of study drug and one postbaseline safety assessment and summarised descriptively. Select adverse events of interest for BRAF/MEK inhibitors were summarised by when they occurred (i.e. in the first 6 months, 6–12 months, 12–18 months and 18–24 months) for patients on treatment for at least 24 months. The incidence of select adverse events associated with BRAF/MEK inhibitors (left ventricular dysfunction, rash, skin papilloma, serous retinopathy, pyrexia and transaminases increased) were summarised by month for all patients over the first 24 months of the study.

2.4. Statistical analyses

An updated analysis was conducted after an additional 12 months' follow-up relative to initial OS analysis with a cut-off date of November 2018. Efficacy end-points were assessed in the intent-to-treat population (defined as all randomly assigned patients). The median durations of the follow-up for OS and PFS were estimated by reverse Kaplan-Meier analysis. The Kaplan-Meier method was used to estimate rates of OS and PFS; the log-rank test, stratified by AJCC stage IIIB, IIIC, IVM1a and IVM1b vs IVM1c and ECOG performance status (0 vs 1), was used to compare distributions. Subgroup analyses of baseline variables and potential prognostic factors, including previous immunotherapy, were also specified. HRs were estimated by the use of Cox proportional hazard regression models. Additional information on the statistical analyses have been previously published [9,10]).

3. Results

3.1. Participants

Baseline patient and disease characteristics are summarised in Table 1. A total of 577 patients were randomised in part 1 of the COLUMBUS study (COMB450: 192; ENCO300: 194 and VEM: 191). Characteristics were similar among the treatment groups and consistent with mutant locally advanced unresectable or metastatic melanoma. Of the 577 patients at baseline, 154 patients (27%) had an elevated LDH level. The disposition of patients in the study is summarised in Table 2. At the time of data cutoff for this analysis (November 2018), 36 patients (19%) were continuing to receive COMBO450, 20 patients (10%) were continuing to receive ENCO300 and 9 patients (5%) were continuing to receive VEM. Discontinuations due to adverse events occurred in 10% of patients in the COMBO450 group, 12% in the ENCO300 group and 14% in the VEM group.

Table 1
Baseline patient and disease characteristics.

Characteristic	COMBO450 n = 192	ENCO300 n = 194	VEM n = 191
Median age (range), years	57 (20–89)	54 (23–88)	56 (21–82)
Male, n (%)	115 (59.9)	108 (55.7)	111 (58.1)
ECOG performance status 0	136 (70.8)	140 (72.2)	140 (73.3)
LDH > ULN	55 (29)	47 (24)	52 (27%)
LDH ≤ ULN	137 (71%)	147 (76%)	139 (73%)
BRAF mutation status			
$BRAF^{V600E}$	170 (89%)	173 (89%)[a]	168 (88%)
$BRAF^{V600K}$	22 (11%)	19 (10%)[a]	23 (12%)
Tumour stage at study entry, n (%)			
IIIB/IIIC	9 (4.7)	6 (3.1)	11 (5.7)
IVM1a	26 (13.5)	29 (14.9)	24 (12.6)
IVM1b	34 (17.7)	39 (20.1)	31 (16.2)
IVM1c	123 (64.1)	120 (61.9)	125 (64.4)
Number of organs involved			
1	47 (24.5)	56 (28.9)	45 (23.6)
2	58 (30.2)	52 (26.8)	59 (30.9)
≥3	87 (45.3)	86 (44.3)	87 (45.6)

COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG = Eastern Cooperative Oncology Group; ENCO300 = encorafenib 300 mg QD; LDH = lactate dehydrogenase; ULN = upper limit of normal; VEM = vemurafenib 960 mg BID.
[a] Two observations were indeterminate.

Table 2
Patient disposition.

Variable	COMBO450 n = 192 n (%)	ENCO300 n = 194 n (%)	VEM n = 191 n (%)
Untreated	0	2 (1.0)	5 (2.6)
Discontinued treatment	156 (81.3)	172 (88.7)	177 (92.7)
Progressive disease	104 (54.2)	101 (52.1)	111 (58.1)
Adverse event	20 (10.4)	24 (12.4)	26 (13.6)
Physician or patient decision[a]	21 (11.0)	35 (23.2)	35 (18.3)
Death	9 (4.7)	1 (0.5)	4 (2.1)
Other[b]	2 (1.0)	1 (0.5)	1 (0.5)
Treatment ongoing[c]	36 (18.8)	20 (10.3)	9 (4.7)

COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300 = encorafenib 300 mg QD; VEM = vemurafenib 960 mg BID.

[a] Physician or patient/guardian decision.

[b] Includes protocol violation, lost to follow-up and new therapy for study indication.

[c] As of the data cut-off date of November 19, 2018.

3.2. Efficacy outcomes

Across arms, the median follow-up for OS was 48.8 months. The median OS for COMBO450 was 33.6 months (95% CI, 24.4–39.2), for ENCO300 was 23.5 months (95% CI, 19.6–33.6) and for VEM was 16.9 months (95% CI, 14.0–24.5; Fig. 1a). Compared with VEM, COMBO450 decreased the risk of death by 39% (HR, 0.61; 95% CI, 0.48–0.79]). A landmark analysis showed a higher rate of OS for COMBO450 at year 1, 2 and 3 (Fig. 1b). At 3 years, the OS rates were 47% for COMBO450, 41% for ENCO300 and 31% for VEM. In general, subgroup analyses for the comparison of COMBO450 with VEM showed point estimates in favour of COMBO450 across various populations (Fig. 2). OS results for the subgroups for LDH high, LDH normal and LDH normal and <3 affected organ sites are shown in Fig. 3. In the LDH normal subgroup, the median OS for COMBO450 was not reached, whereas the median OS for VEM was 24.5 months. Similarly, for patients with LDH normal and <3 organ sites, the median OS for COMBO450 was not reached, whereas the median OS for VEM was 28.1 months. The median OS for the high LDH subgroup was 11.4 months for COMBO450 and 9.6 months for VEM (HR,0.93; [95% CI, 0.62, 1.39]).

A summary of patients receiving antineoplastic therapy after study drug discontinuation by line of therapy for each treatment arm is shown in Table 3. After study drug discontinuation, systemic treatments were received by 82 (53%) of 156 patients in the COMBO450 group, 107 (62%) of 172 in the ENCO300 group and 122 (69%) of 177 in the VEM group (Table 3). Anti-cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and anti–programmed death 1 or anti–programmed death ligand 1 immunotherapies were the most frequent first and second subsequent regimens and were received by approximately the same proportion of patients in all groups. Approximately half of the patients who received immunotherapy as the first post-study therapy were treated with anti–CTLA-4 monotherapy (i.e. ipilimumab) across all study arms (Table 3).

At the time of data cutoff, disease progression or death had occurred in 350 of 577 patients (61%). The updated median PFS by central review was 14.9 months (95% CI, 11.0–20.2) for COMBO450, 9.6 months (95% CI, 7.4–14.8) for ENCO300 and 7.3 months (95% CI, 5.6–7.9) for VEM. The PFS was longer for COMBO450 vs VEM (HR, 0.51; 95% CI, 0.39–0.67). A landmark analysis showed a higher rate of PFS for COMBO450 at year 1, 2 and 3 (Fig. 4). At 3 years, the PFS rates were 29% for COMBO450, 25% for ENCO300 and 14% for VEM.

ORR results were higher for COMBO450 than for VEM (Table 4). Confirmed overall response by masked independent central review was observed in 64% (95% CI, 56–70) of 192 patients in the COMBO450 group, 52% (95% CI, 44–59) of 194 patients in the ENCO300 group and 41% (95% CI, 34–48) of 191 patients in the VEM group (Table 4). By local review, a confirmed overall response was observed in 76% (95% CI, 69–81) patients in the COMBO450 group, in 58% (95% CI, 51–65) in the ENCO300 group and in 49% (95% CI, 42–57) in the VEM group. The median duration of response was analysed by central and local reviews. By central review, it was 18.6 months (95% CI, 12.7–24.1) in the COMBO450 group, 15.5 months (95% CI, 11.1–28.6) in the ENCO300 group and 12.3 months (95% CI, 6.9–14.5) in the VEM group. Duration of response assessed by local investigator was similar.

3.3. Safety

A total of 68%, 68% and 66% of patients experienced grade 3/4 adverse events in the COMBO450, ENCO300 and VEM groups, respectively (Table 5). Adverse event associated with BRAF inhibitors and MEK inhibitors did not increase substantially in time since the updated analysis (Fig. 5). Adverse events led to discontinuation in 16%, 15% and 17% and dose reduction/interruption in 55%, 71% and 62% for COMBO450, ENCO300 and VEM, respectively. On-treatment deaths occurred in 13%, 8% and 11% of patients for COMBO450, ENCO300 and VEM, respectively.

Select adverse events of interest for BRAF/MEK inhibitors occurring in the first 6 months, 6–12 months, 12–18 months and 18–24 months of treatment with COMBO450 are shown in Table 6 (only patients who received treatment for at least 24 months were included in the analysis [n = 59]). Across the adverse events evaluated, patients had less burden of toxicity later in the 2-year analysis. Fig. 6 shows the incidence of adverse events for select adverse events associated with BRAF/MEK inhibitors (left ventricular dysfunction, rash, skin

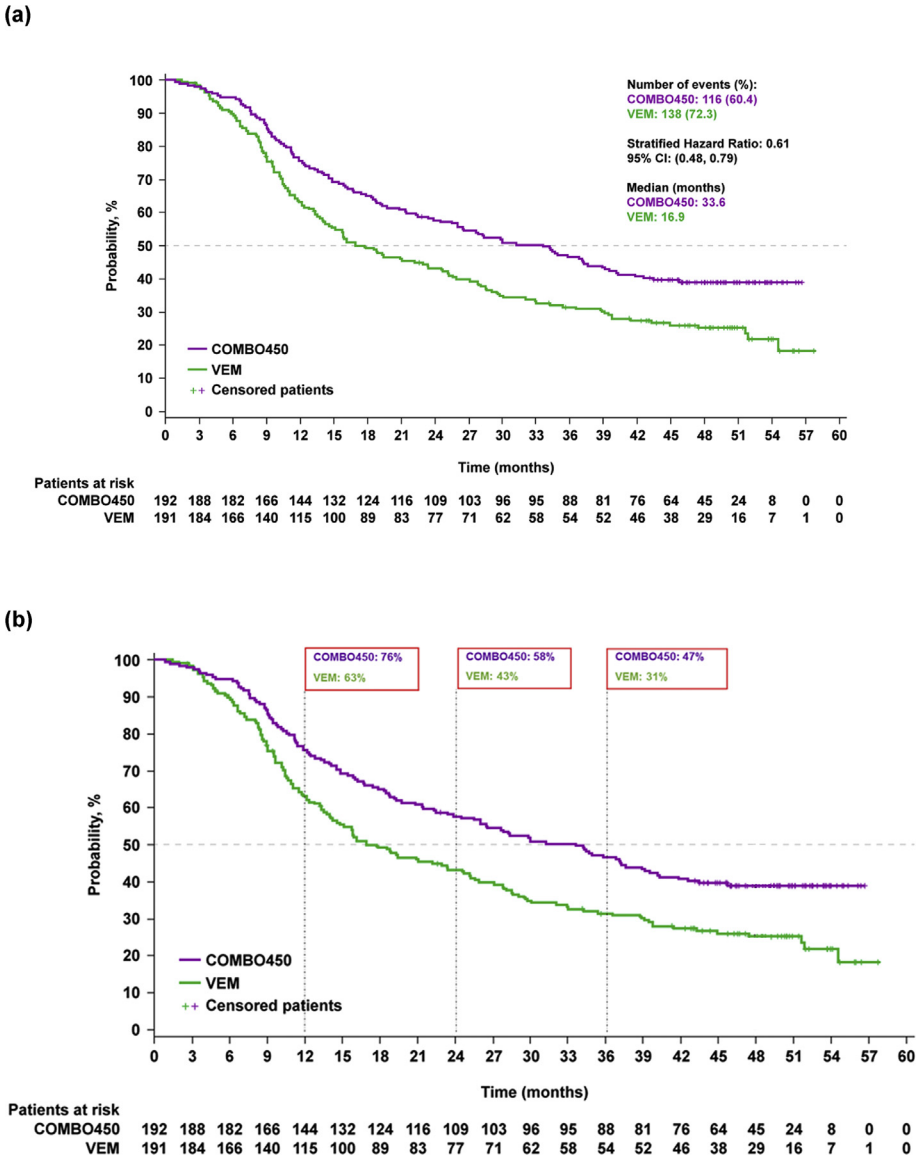

Fig. 1. Overall survival (a) and landmark analysis (b): COMBO450 vs VEM. COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; VEM = vemurafenib 960 mg BID.

papilloma, serous retinopathy, pyrexia and transaminases increased) by month for all patients over the first 24 months of the study. The incidence of some of these adverse events generally appears to be less frequent over time.

4. Discussion

These landmark analyses of the phase 3, randomised COLUMBUS trial in patients with *BRAF*-mutant melanoma treated with encorafenib plus binimetinib show improved OS and PFS for COMBO450 vs VEM in a follow-up analysis. The current updated analyses confirmed previous findings of prolonged OS for COMBO450 vs VEM: 33.6 vs 16.9 months and PFS: 14.9 vs 7.3 months, with similar results across a broad range of subgroups, although patients with elevated LDH seem to have limited benefit. Safety results were consistent with the known tolerability profile of COMBO450, with nausea, diarrhoea, and vomiting as the most common adverse events. No new safety concerns were noted in this update, and patients maintaining response have less burden of toxicity in the later years. These results for COMBO450 from the COLUMBUS trial demonstrate the potential for a long-term benefit in patients with advanced *BRAF* V600–mutated melanoma.

The updated analysis presented in this manuscript is consistent with previous reports of the COLUMBUS study [9,10]), with a durable benefit in patients with *BRAF*-mutant metastatic melanoma. Based on subgroup analysis and multivariable regression modelling

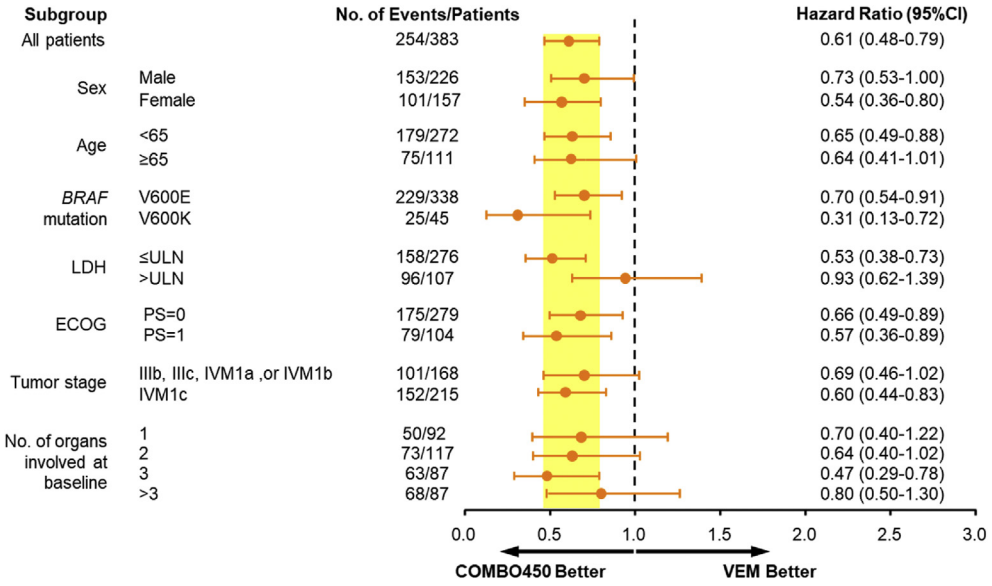

Fig. 2. Overall survival subgroups: COMBO450 vs VEM. COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; VEM = vemurafenib 960 mg BID.

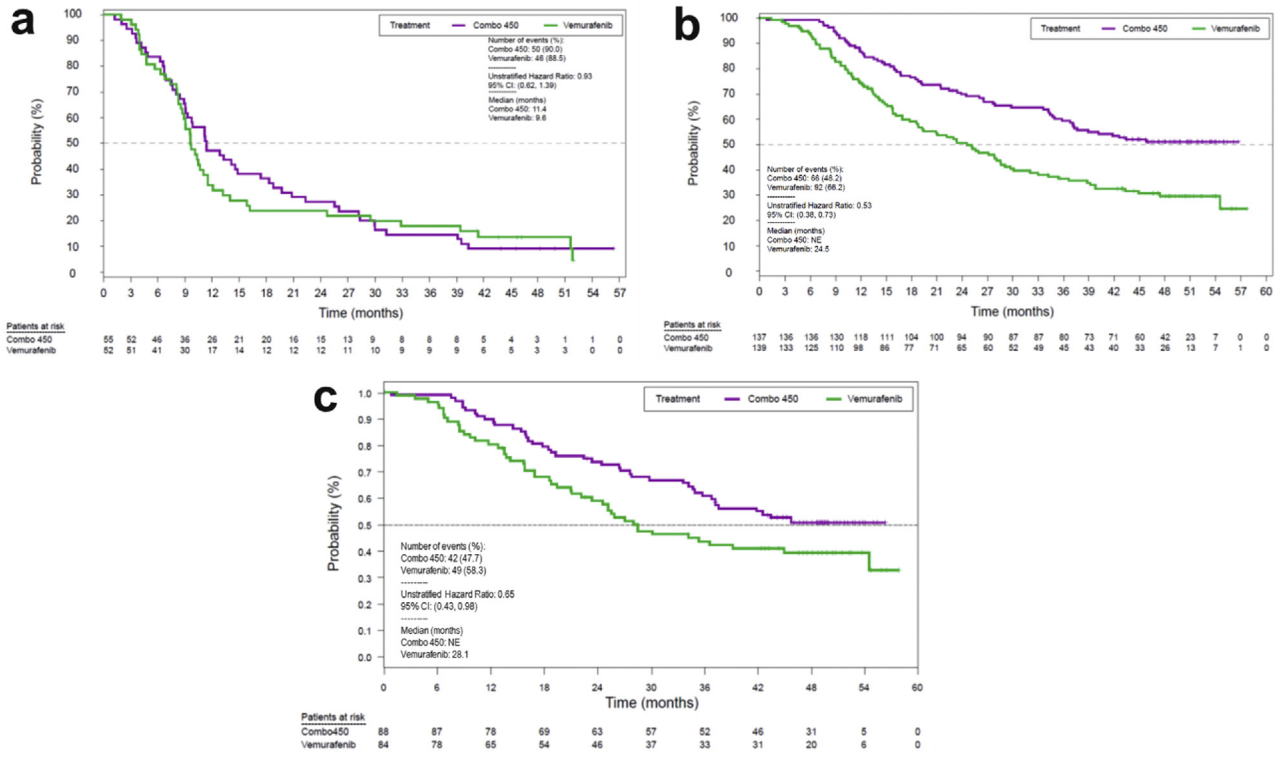

Fig. 3. Overall survival subgroups: (a). LDH high; (b). LDH normal; and (c). LDH normal and <3 metastatic organ sites. LDH = lactate dehydrogenase.

to account for prespecified baseline covariates, COMBO450 showed consistent improvement relative to VEM across a broad range of patients. As expected, patients with normal LDH performed better than patients with high LDH in all treatment groups, as seen in previous trials involving other BRAF/MEK inhibitors [2,11–13]. Results in the high LDH subgroup favoured COMBO450 relative to VEM (median OS for COMBO450 = 11.4 months; VEM = 9.6 months). Additional research is needed to understand how treatment for this group of patients can be optimised. As noted previously, the types of systemic treatment received after study drug discontinuation were generally similar in all three groups, with slightly higher use of

Table 3
Systemic treatment after study drug discontinuation.

Variable	COMBO450 N = 156 n (%)	ENCO300 N = 172 n (%)	VEM N = 177 n (%)
Any regimen	82 (52.6)	107 (62.2)	122 (68.9)
First line after COLUMBUS study treatment	82 (52.6)	107 (62.2)	122 (68.9)
At least one immunotherapy	59 (37.8)	54 (31.4)	60 (33.9)
Anti–CTLA-4	29 (18.6)	25 (14.5)	29 (16.4)
Anti–CTLA-4 +Anti-PD1	4 (2.6)	0	1 (0.6)
Anti-PD1	25 (16.0)	28 (16.3)	28 (15.8)
Other	1 (0.6)	1 (0.6)	2 (1.1)
At least one targeted therapy	16 (10.3)	37 (21.5)	49 (27.7)
BRAFi	9 (5.8)	13 (7.6)	12 (6.8)
BRAFi + MEKi	5 (3.2)	23 (13.4)	29 (16.4)
Other	2 (1.3)	1 (0.6)	8 (4.5)
At least one chemotherapy	8 (5.1)	17 (9.9)	15 (8.5)
Second line after COLUMBUS study treatment	30 (19.2)	34 (19.8)	56 (31.6)
At least one immunotherapy	17 (10.9)	23 (13.4)	32 (18.1)
Anti–CTLA-4	4 (2.6)	7 (4.1)	5 (2.8)
Anti–CTLA-4 +Anti-PD1	1 (0.6)	3 (1.7)	2 (1.1)
Anti-PD1	11 (7.1)	12 (7.0)	22 (12.4)
Other	1 (0.6)	1 (0.6)	3 (1.7)
At least one targeted therapy	8 (5.1)	4 (2.3)	19 (10.7)
BRAFi	1 (0.6)	0	7 (4.0)
BRAFi + MEKi	5 (3.2)	3 (1.7)	8 (4.5)
Other	2 (1.3)	1 (0.6)	4 (2.3)
At least one chemotherapy	6 (3.8)	7 (4.1)	7 (4.0)
Third line or later after COLUMBUS study treatment	13 (8.3)	12 (7.0)	18 (10.2)
At least one immunotherapy	10 (6.4)	5 (2.9)	8 (4.5)
Anti–CTLA-4	0	0	3 (1.7)
Anti–CTLA-4 +Anti-PD1	2 (1.3)	2 (1.2)	1 (0.6)
Anti-PD1	8 (5.1)	2 (1.2)	4 (2.3)
Other	1 (0.6)	1 (0.6)	0
At least one targeted therapy	3 (1.9)	7 (4.1)	12 (6.8)
BRAFi	1 (0.6)	1 (0.6)	2 (1.1)
BRAFi + MEKi	2 (1.3)	5 (2.9)	9 (5.1)
Other	1 (0.6)	1 (0.6)	2 (1.1)
At least one chemotherapy	3 (1.9)	4 (2.3)	5 (2.8)

COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300 = encorafenib 300 mg QD; VEM = vemurafenib 960 mg BID; anti-PD1 = anti–programmed death 1; anti–CTLA-4 = anti-cytotoxic T-lymphocyte–associated protein 4; COLUMBUS.

BRAF/MEK inhibitor regimens in the encorafenib and vemurafenib groups, as expected in patients who progress on monotherapy [10]. Of the 33% patients in the trial who received immunotherapy as the first post-study therapy, approximately half were treated with anti–CTLA-4 monotherapy (i.e. ipilimumab) across all study arms. Subsequent therapy does not appear to account for observed differences in overall survival observed in the COLUMBUS group.

The safety profile of COMBO450 in the updated analysis is also consistent with previous observations. The incidence of pyrexia and photosensitivity with encorafenib plus binimetinib appear to be lower than shown in previous trials of established BRAF/MEK inhibitor combinations [2,3,13]. As noted with temporal analysis of select adverse events over the course of the study, patients appeared to have less burden of toxicity later in the 2-year analysis (i.e. as the study progressed). This observation is similar to what has been observed in a previous BRAF/MEK inhibitor study analysis [14].

In this analysis, the PFS curve for encorafenib plus binimetinib appears to begin to level out in the later years, suggesting a potential stabilisation of patients' disease (i.e. the PFS rates for COMBO450 were 37% and 29% for years 2 and 3, respectively). A similar observation was noted by Robert *et al.* in a pooled analysis of the phase 3 dabrafenib-trametinib melanoma trials, in which they observed PFS rates of 31%, 24%, 21% and 19% for years 2 through 5 [11]. No direct comparisons of encorafenib plus binimetinib with other BRAF/MEK inhibitor combinations are available. Although the COLUMBUS trial was not designed to compare encorafenib plus binimetinib with other BRAF/MEK inhibitor regimens, the results compare favourably to prior studies with other agents. For example, the median PFS in phase 3 trials evaluating dabrafenib-trametinib (COMBI-d and COMBI-v trials [2,3,11]) and vemurafenib-cobimetinib (coBRIM [13]) ranged from 11.0 to 12.3 months. In this update, the median PFS for encorafenib plus binimetinib was 14·9 months (95% CI, 11.0–20.2). In preclinical studies, encorafenib, dabrafenib and vemurafenib all inhibit *BRAF* V600E kinase activity at similar concentrations. However, encorafenib has a longer dissociation half-life than for dabrafenib or vemurafenib (>30 h vs 2 h vs 0–5 h, respectively), resulting in longer inhibition of pERK [6]. Increased antitumour activity in *BRAF* V600–mutant cell lines was also observed for encorafenib in preclinical studies [4,6]. These observations appear to support the hypothesis that extended pathway inhibition can lead to improved clinical outcomes.

There are several limitations of this analysis that should be noted. First, OS was not the primary endpoint of the study; however, OS was a key efficacy endpoint and the comparison of the COMBO450 group with the VEM group was included in the testing hierarchy in COLUMBUS. These data will continue to be monitored and additional updates will be published as more data become available. Finally, the COLUMBUS study did not enrol patients with metastatic brain metastasis, and therefore data on this subgroup are not available in this updated analysis. A recent retrospective analysis showed combination therapy with encorafenib plus binimetinib elicited intracranial activity in patients with *BRAF*-mutant melanoma brain metastases, including in patients previously treated with BRAF/MEK inhibitors [15]. This population is currently being prospectively evaluated in a phase 2 trial to further evaluate efficacy and safety of two dosing regimens of encorafenib plus binimetinib in patients with *BRAF* V600–mutant melanoma brain metastases (NCT03911869).

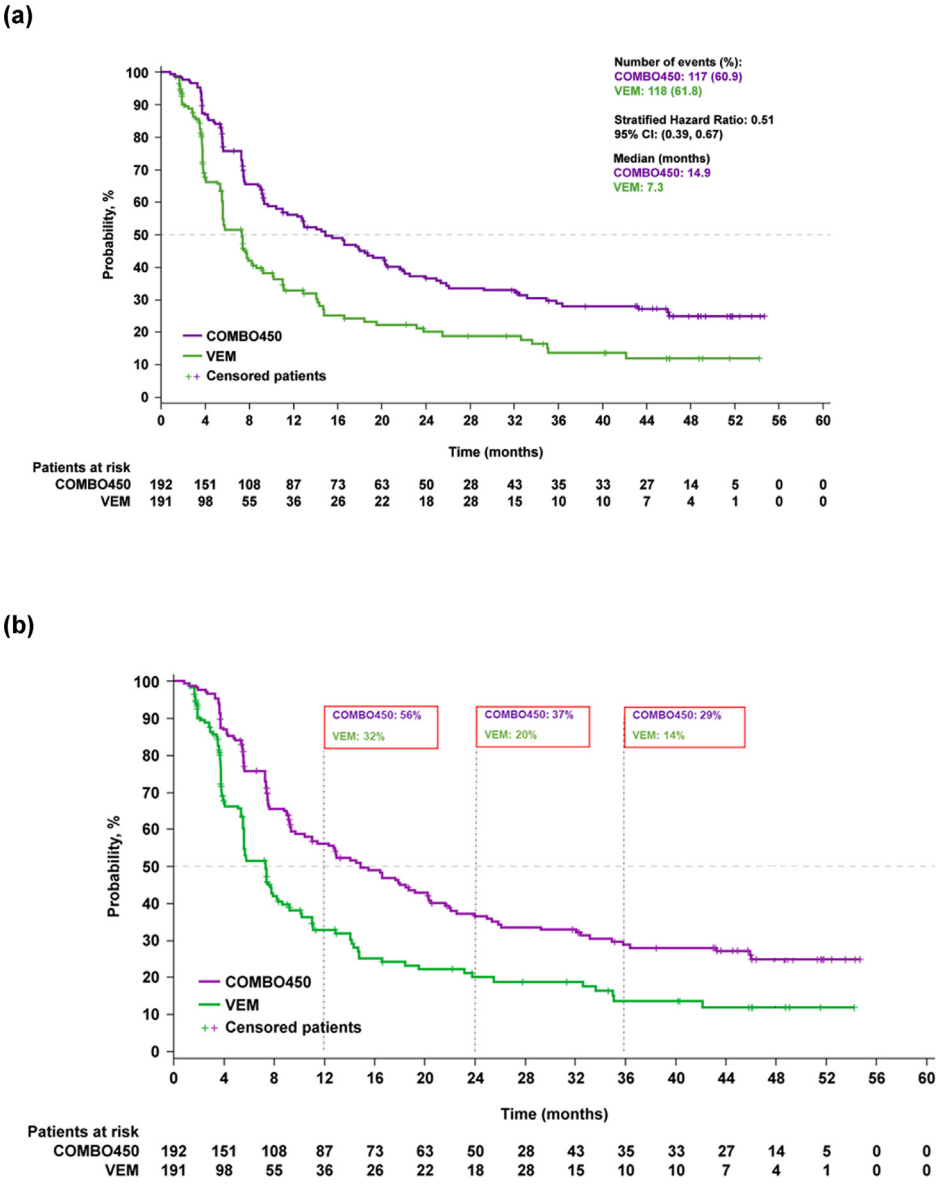

Fig. 4. PFS (a) and landmark analysis (b): COMBO450 vs VEM. COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; VEM = vemurafenib 960 mg BID.

In conclusion, patients treated with encorafenib plus binimetinib had longer PFS and OS than those treated with vemurafenib, with landmark analyses showing consistent improved OS and PFS for COMBO450 vs VEM for each year. Safety results were consistent with the known tolerability profile of COMBO450, and the toxicity burden was reduced over time. These data reinforce encorafenib plus binimetinib as an important treatment option for patients with *BRAF*-mutant melanoma. Trials are planned and underway to further assess the use of encorafenib and binimetinib in various patient populations, including as earlier line treatment and in high-risk patients.

Conflict of interest statement

P.A.A. served a consulting or advisory role for BMS, Roche-Genentech, MSD, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, Newlink Genetics, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes. P.A.A. received research funds from BMS, Roche-Genentech, Array and received travel fees from MSD. R.D. had intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun

Table 4
Confirmed response rates.

Variable	COMBO450 N = 192 n (%)		ENCO300 N = 194 n (%)		VEM N = 191 n (%)	
	Central review	Local review	Central review	Local review	Central review	Local review
Best overall response						
Complete response	24 (12.5)	40 (20.8)	14 (7.2)	20 (10.3)	16 (8.4)	16 (8.4)
Partial response	98 (51.0)	105 (54.7)	86 (44.3)	93 (47.9)	62 (32.5)	78 (40.8)
Stable disease	55 (28.6)	33 (17.2)	63 (32.5)	55 (28.3)	77 (40.3)	66 (34.5)
Progressive disease[a]	15 (7.8)	14 (7.3)	31 (16.0)	26 (13.4)	36 (18.8)	31 (16.3)
Overall response[b]	122 (63.5)	145 (75.5)	100 (51.5)	113 (58.2)	78 (40.8)	94 (49.2)
95% CI	(56.3, 70.4)	(68.8, 81.4)	(44.3, 58.8)	(51.0, 65.3)	(33.8, 48.2)	(41.9, 56.5)
Disease control[c]	177 (92.2)	178 (92.7)	163 (84.0)	168 (86.6)	155 (81.2)	160 (83.8)
95% CI	(87.4, 95.6)	(88.1, 96.0)	(78.1, 88.9)	(81.0, 91.1)	(74.9, 86.4)	(77.8, 88.7)

Data are n (%) or n (%; 95% CI) in the efficacy population. *Includes patients with non-measurable disease and a status of non-complete response or non-progressive disease. CI = confidence interval; COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300 = encorafenib 300 mg QD; VEM = vemurafenib 960 mg BID.

[a] Includes patients with best response of unknown or no assessment.

[b] Overall response was defined as complete response plus partial response.

[c] Disease control defined as the proportion of patients with a best overall response of complete response, partial response, stable disease, or non-complete response or non-progressive disease.

Pharma, Sanofi and Catalym outside the submitted work. H.J.G. reports receiving consulting fees from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen and Pierre Fabre and research funding from Bristol-Myers Squibb, Merck Sharp & Dohme and Roche outside the submitted work. K.T.F. served as a member of the Board of Directors for Clovis Oncology*, Strata Oncology*, Vivid Biosciences*, Checkmate Pharmaceuticals ; served as a member of the Corporate Advisory Board for X4 Pharmaceuticals*, PIC Therapeutics*; served as a member of the Scientific Advisory Board for Sanofi, Amgen, Asana, Adaptimmune, Fount *, Aeglea, Array BioPharma, Shattuck Labs *, Tolero, Apricity *, Oncoceutics*, Fog Pharma

Table 5
Adverse events occurring in ≥20% of patients.

Preferred term	COMBO450 N = 192		ENCO300 N = 192		VEM N = 186	
	All grades n (%)	Grade III/IV n (%)	All grades n (%)	Grade III/IV n (%)	All grades n (%)	Grade III/IV n (%)
Total	189 (98.4)	131 (68.2)	191 (99.5)	130 (67.7)	186 (100)	122 (65.6)
Nausea	84 (43.8)	4 (2.1)	74 (38.5)	8 (4.2)	65 (34.9)	3 (1.6)
Diarrhea	74 (38.5)	5 (2.6)	29 (15.1)	4 (2.1)	64 (34.4)	4 (2.2)
Vomiting	61 (31.8)	4 (2.1)	56 (29.2)	9 (4.7)	30 (16.1)	2 (1.1)
Fatigue	57 (29.7)	4 (2.1)	50 (26.0)	1 (0.5)	57 (30.6)	4 (2.2)
Arthralgia	55 (28.6)	2 (1.0)	87 (45.3)	18 (9.4)	86 (46.2)	11 (5.9)
Blood creatine phosphokinase increased	50 (26.0)	15 (7.8)	2 (1.0)	0	4 (2.2)	0
Headache	49 (25.5)	4 (2.1)	55 (28.6)	6 (3.1)	37 (19.9)	2 (1.1)
Constipation	48 (25.0)	0	31 (16.1)	0	13 (7.0)	1 (0.5)
Asthenia	42 (21.9)	3 (1.6)	42 (21.9)	5 (2.6)	35 (18.8)	8 (4.3)
Pyrexia	38 (19.8)	7 (3.6)	32 (16.7)	2 (1.0)	53 (28.5)	0
Dry skin	31 (16.1)	0	58 (30.2)	1 (0.5)	43 (23.1)	0
Myalgia	31 (16.1)	0	55 (28.6)	19 (9.9)	34 (18.3)	1 (0.5)
Rash	31 (16.1)	3 (1.6)	40 (20.8)	4 (2.1)	56 (30.1)	6 (3.2)
Hyperkeratosis	29 (15.1)	1 (0.5)	77 (40.1)	7 (3.6)	54 (29.0)	0
Alopecia	28 (14.6)	0	108 (56.3)	0	70 (37.6)	0
Pruritus	24 (12.5)	1 (0.5)	42 (21.9)	1 (0.5)	20 (10.8)	0
Pain in extremity	23 (12.0)	2 (1.0)	43 (22.4)	2 (1.0)	27 (14.5)	2 (1.1)
Decreased appetite	19 (9.9)	0	40 (20.8)	1 (0.5)	36 (19.4)	2 (1.1)
Palmoplantar keratoderma	19 (9.9)	0	51 (26.6)	4 (2.1)	33 (17.7)	2 (1.1)
Palmar-plantar erythrodysaesthesia syndrome	14 (7.3)	0	99 (51.6)	26 (13.5)	26 (14.0)	2 (1.1)
Keratosis pilaris	9 (4.7)	0	33 (17.2)	0	43 (23.1)	0
Photosensitivity	7 (3.6)	1 (0.5)	7 (3.6)	0	47 (25.3)	2 (1.1)

COMBO450 = encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300 = encorafenib 300 mg QD; VEM = vemurafenib 960 mg BID.

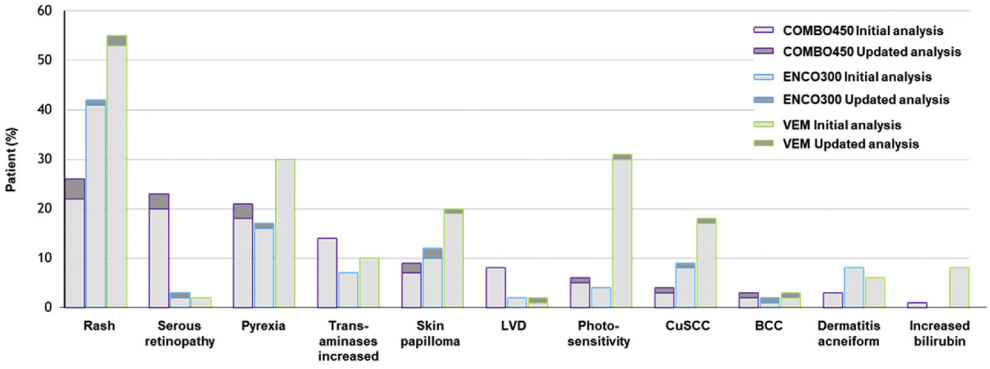

Fig. 5. Adverse events associated with BRAF inhibitors and MEK inhibitors.

*, Neon, Tvardi *, served as a consultant Novartis, Genentech, BMS, Merck, Takeda, Verastem, Boston Biomedical, Pierre Fabre, Cell Medica, Debiopharm*; and as a stock shareholder. A.A. has received honoraria from, had a consulting or advisory role with or been a member of the speakers bureau for Novartis, Roche, Merck, Merck Sharp & Dohme, Bristol-Myers Squibb, Pierre Fabre, Sanofi and Amgen outside the submitted work and has received travel expenses from the same companies. M.M. has received personal fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis and Pierre Fabre outside the submitted work. G.L. has received consulting and advisory board fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Amicus, Boehringer-Ingelheim and Novartis outside the submitted work. C.G. has received personal fees and research funding from Novartis and Pierre Fabre during the conduct of the study. C.G. has received personal fees for presentations and consulting or advisory roles from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, NeraCare, Philogen, Roche and Sanofi and research funding from Bristol-Myers Squibb, Neracare, Roche and Sanofi outside the submitted work. D.S. has received personal fees and patients' fees from Pierre Fabre and Array BioPharma during the conduct of the study. D.S. has received honoraria and travel expenses from, has a consulting or advisory role with, been a member of the speakers bureau for and received personal fees from, Amgen, Boehringer Ingelheim, LEO Pharma, Roche, Novartis, Hexal, InflaRx, Helsinn, GI Innovation, Immunocore, Sanofi, Neracare, Merck Sharp & Dohme, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, Pierre Fabre, Merck-EMD, Pfizer, Philogen, Ultimovacs and Sun Pharma, all outside of the submitted work. I.K. is an advisory board member for and has received travel expenses from Bristol-Myers Squibb, Novartis and Merck Sharp & Dohme during the conduct of the study. R.G. received research support from Pfizer, Johnson&Johnson, Novartis, Amgen, Merck Serono; received honoraria for lectures from RochePharma, Bristol-Myers Squibb, Novartis, MSD, Almirall-Hermal, Amgen, Merck Serono, Pierre Fabre, AstraZeneca, SUN; received honoraria for advice from RochePharma, Bristol-Myers Squibb, Novartis, MSD, Almirall-Hermal, Amgen, Takeda, Pierre Fabre, Merck Serono, 4SC, Incyte, SUN; Support for participation in meetings from Bristol-Myers Squibb, Pierre Fabre, Merck Serono, SUN, RochePharma. J.W.B.dG. received personal fees from Roche, Bristol-Myers

Table 6
Select adverse events of interest occurring in the first 6 months, 6–12 months, 12–18 months and 18–24 months for patients on COMBO450 for at least 24 months.

Category	0 - <6 months n (%)	6 to <12 months n (%)	12 to <18 months n (%)	18 to <24 months n (%)
Left ventricular dysfunction	3 (5.1)	2 (3.4)	2 (3.4)	1 (1.7)
Rash	9 (15.3)	6 (10.2)	3 (5.1)	2 (3.4)
Basal cell carcinoma	1 (1.7)	0 (–)	0 (–)	0 (–)
Skin papilloma	3 (5.1)	3 (5.1)	0 (–)	2 (3.4)
Serous retinopathy	9 (15.3)	5 (8.5)	7 (11.9)	3 (5.1)
Photosensitivity	3 (5.1)	0 (–)	0 (–)	2 (3.4)
Pyrexia	8 (13.6)	4 (6.8)	4 (6.8)	1 (1.7)
Transaminases increased	6 (10.2)	1 (1.7)	1 (1.7)	0 (–)
Cutaneous squamous cell carcinoma	1 (1.7)	0 (–)	1 (1.7)	1 (1.7)
Dermatitis acneiform	1 (1.7)	2 (3.4)	1 (1.7)	0 (–)
Blood bilirubin increased	0 (–)	0 (–)	1 (1.7)	0 (–)

The total number of patients on COMBO450 treatment for at least 24 months is 59, which is the denominator of each category. If a patient had the same AE occur in multiple time ranges, the patient is counted in each of the time ranges. AE = adverse event.

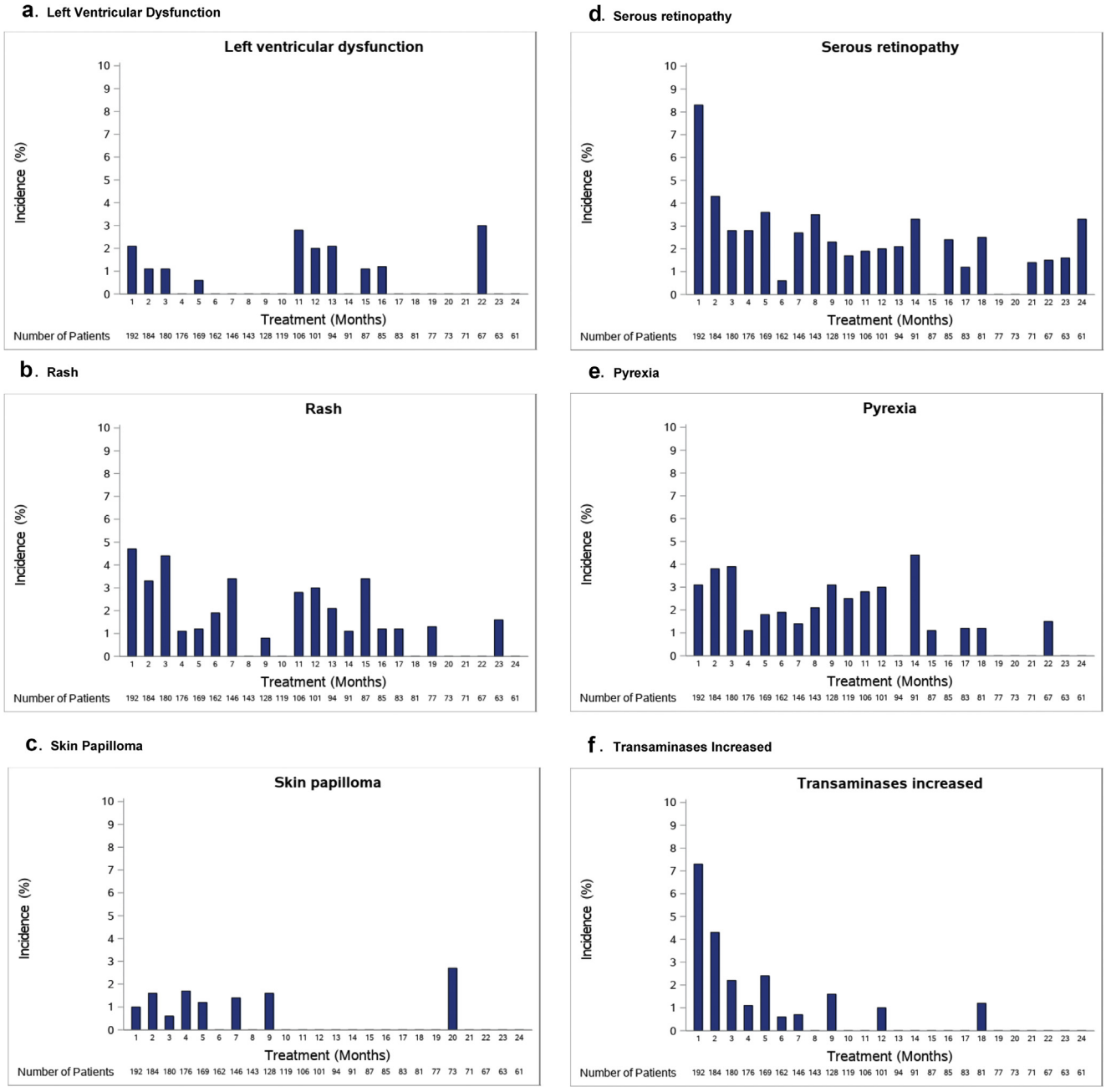

Fig. 6. Adverse event incidence by month for (a) left ventricular dysfunction, (b) rash, (c) skin papilloma, (d) serous retinopathy, (e) pyrexia, and (f) transaminase increased.

Squibb, Pierre Fabre, Servier, Novartis and Merck Sharp & Dohme outside the submitted work. C.L. reports receiving personal fees from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, LEO Pharma, Amgen, Biontech and Sun Pharma outside the submitted work. A.G. is an employee at Pfizer Inc. M.D.P. is an employee at Pfizer Inc. C.R. is a consultant for Pierre Fabre, Roche, Novartis, Bristol-Myers Squibb, Merck, Array BioPharma, Merck Serono and Amgen outside the submitted work.

Acknowledgements

The authors would like to thank all of the individuals who enrolled in COLUMBUS, as well as their family, caregivers, and friends who supported them. These analyses would not be possible without all of the hard work and contributions from the dedicated investigators in this trial. The authors acknowledge JD Cox, PhD and Mayville Medical Communications for editorial support.

References

[1] Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.

[2] Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30–9.

[3] Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386:444–51.

[4] Koelblinger P, Thuerigen O, Dummer R. Development of encorafenib for BRAF-mutated advanced melanoma. Curr Opin Oncol 2018;30:125–33.

[5] Stuart DD, Li N, Poon DJ, et al. Preclinical profile of LGX818: a potent and selective RAF kinase inhibitor. Cancer Res 2012;72. Abstract 37906.

[6] Delord JP, Robert C, Nyakas M, et al. Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF- mutant melanoma. Clin Cancer Res 2017;23(18):5339–48.

[7] Holderfield M, Merritt H, Chan J, Wallroth M, Tandeske L, Zhai H, et al. RAF inhibitors activate the MAPK pathway by relieving inhibitory autophosphorylation. Cancer Cell 2013;23:594–602.

[8] Ascierto PA, Schadendorf D, Berking C, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, pen-label phase 2 study. Lancet Oncol 2013;14:249–56.

[9] Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;19(5):603–15.

[10] Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19(10):1315–27.

[11] Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019;381(7):626–36.

[12] Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 2017;28:1631–9.

[13] Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248–60.

[14] Breno B, Ascierto PA, McArthur, et al. Adverse event incidence rates with cobimetinib combined with vemurafenib treatment: extended follow-up of the phase 3 coBRIM study. J Clin Oncol 2016;34(15). 9533-9533.

[15] Holbrook K, Lutzky J, Davies MA, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: a case series. Cancer; 2019 Oct 28. https://doi.org/10.1002/cncr.32547 [Epub ahead of print].